Gestational Diabetes Mellitus

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Published in:
Journal of diabetes

DOI:
10.1111/1753-0407.12422

Journal of Diabetes

Journal of Diabetes **8** (2016), 770–781

REVIEW ARTICLE

Gestational Diabetes Mellitus:current knowledge and unmet needs

Highlights
1. There is considerable controversy in the literature surrounding the diagnosis and treatment (including diet, insulin therapy, and oral blood glucose lowering agents) of gestational diabetes mellitus, as well as the possible long-term consequences for the offspring.
2. Worldwide different diagnostic criteria are used and discussion remains on the efficiency, and safety, of treatment modalities.
3. There is clearly more need for GDM research. Gestational diabetes mellitus is a global health concern, because its prevalence is high and on the increase, but also because of the potential implications for the health of mothers and their offspring.

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Received 8 February 2016; revised 30 March 2016; accepted 23 April 2016.

doi: 10.1111/1753-0407.12422

Abstract

Gestational diabetes mellitus (GDM) is a global health concern, not only because its prevalence is high and on the increase, but also because of the potential implications for the health of mothers and their offspring. Unfortunately, there is considerable controversy in the literature surrounding the diagnosis and treatment of GDM, as well as the possible long-term consequences for the offspring. As a result, worldwide there is a lack of uniformly accepted diagnostic criteria and the advice regarding the treatment of GDM, including diet, insulin therapy, and the use of oral blood glucose-lowering agents, is highly variable. In this review we provide an overview of the important issues in the field of GDM, including diagnostic criteria, different treatment regimens available, and the long-term consequences of GDM in the offspring.

Keywords: diagnosis, diet, gestational diabetes mellitus, insulin, oral blood glucose-lowering agents.

Introduction

Historically, gestational diabetes mellitus (GDM) was defined as any degree of glucose intolerance with an onset or first recognition during pregnancy. According to the American Diabetes Association (ADA),[1] GDM is diabetes mellitus (DM) diagnosed in the second or third trimester of pregnancy that does not clearly meet the criteria of overt DM. For women diagnosed with GDM in the first trimester of pregnancy, pre-existing DM should be strongly considered.[1] Gestational diabetes mellitus affects up to 14 % of all pregnancies, depending on the diagnostic criteria used and the population studied.[2] Given the fact that both obesity and DM are now worldwide epidemics, the prevalence of GDM is still increasing.[2–4]

Untreated GDM carries a risk for both the mother and child and is associated with serious short- and long-term consequences, including neonatal and obstetric complications during pregnancy and childbirth (e.g. macrosomia, birth injury, cesarean section[5–7]) and a predisposition to obesity and DM in the offspring in later life.[8–10] Fortunately, studies have shown that many of these consequences can be reduced by early detection

and intervention.[11,12] However, worldwide there is still a lack of agreement on the best way to diagnose and treat GDM. Different diagnostic criteria are used, and many countries use their own recommendations. As a result, discussion remains on the efficiency, and safety, of treatment modalities for GDM, including the use of oral blood glucose-lowering agents, as well as the possible short- and long-term consequences for the offspring.

Herein we describe both the current knowledge regarding GDM and the unmet needs of this condition. We review the diagnostic criteria, different treatment regimens available, and the consequences of GDM in the offspring.

Diagnostic criteria

The original diagnostic criteria for GDM were established in 1964 by O'Sullivan and Mahan.[13] Their criteria were based on a 3-h 100-g oral glucose tolerance test (OGTT) and were chosen to identify women at high risk for development of diabetes after pregnancy.[13] In 1979–80, the 2-h 75-g OGTT was introduced as diagnostic test for non-pregnant diabetic individuals, and the World Health Organization (WHO) advised that this be used to diagnose diabetes in pregnant women, with cut-off values for the diagnosis of GDM being fasting plasma glucose (FPG) ≥7.8 mmol/L and 2-h glucose levels ≥11.1 mmol/L.[14,15] In 1997, the ADA proposed to lower the FPG from 7.8 to 7.0 mmol/L for non-pregnant diabetic individuals.[16] Two years later, the WHO 1999 report on the definition, screening, and diagnosis of GDM was the first step to creating a universal guideline for GDM.[17] In that report, the same fasting glucose values for pregnant women were recommended as proposed by the ADA.[17] These diagnostic criteria were not specifically intended to identify increased risk of adverse neonatal and maternal outcomes.[18]

For decades, the degree of hyperglycemia that was associated with increased risk of adverse neonatal and maternal outcomes remained uncertain. In 2008, the multinational prospective observational Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported on the associations between FPG and 1- and 2-h plasma glucose values during an OGTT and the risk of adverse neonatal and maternal outcomes.[19] More than 25 000 non-diabetic women with singleton pregnancies underwent a 75-g OGTT at 24–32 weeks gestation. The study demonstrated a continuous association of maternal glucose levels with increased rates of both the predefined primary adverse pregnancy outcomes (i.e. birth weight > 90th percentile and cord blood serum C-peptide levels >90th percentile) and the secondary outcomes (i.e. premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and pre-eclampsia).[19] As a result of these findings and those from earlier observational studies,[5,20–23] the diagnostic criteria of GDM were reconsidered worldwide, and guidelines were adapted to include these more stringent criteria. In 2010, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) published new criteria for the diagnosis of GDM, which recommended the following 75-g OGTT glycemic thresholds: fasting value ≥5.1 mmol/L (92 mg/dL); 1-h value ≥10.0 mmol/L (180 mg/dL); and 2-h value ≥8.5 mmol/L (153 mg/dL).[18] These values were chosen because they predict an increased risk of adverse pregnancy outcomes (defined as a 75 % higher chance of adverse outcomes vs normal glucose values). For the other adverse outcomes of the HAPO study, no threshold risk could be identified.[18]

The IADPSG criteria were adopted by the ADA in 2010[24] and by the WHO in 2013.[14] However, the ADA did not follow the one-step diagnostic approach recommended by the IADPSG and left the door open for the two-step screening strategy based on the National Institutes of Health (NIH) consensus conference report.[24,25] The IADPSG's one-step screening strategy involves the use of a 75-g OGTT, whereby GDM is diagnosed on the basis of one abnormal value for either the fasting or the 2-h glucose level. The two-step screening strategy makes use of a non-fasting 50-g glucose challenge test, whereby an abnormal test result (i.e. 1-h value ≥7.8 mmol/L) is followed by a 100-g OGTT. Gestational diabetes mellitus is then diagnosed on the basis of two abnormal values in this 100-g OGTT for the fasting, 1-, 2-, or 3-h glucose levels, using either the Carpenter and Coustan criteria[26] or the National Diabetes and Data Group criteria (Table 1).[27]

Worldwide, there is a lack of uniformly accepted diagnostic criteria. The different criteria used by different expert groups are summarized in Table 1. The main discrepancies in these guidelines relate to the use of FPG values that are higher than those of the IADPSG criteria. However, studies have shown that global adoption of the IADSPG criteria would lead to an increase in the prevalence of GDM, which would result in a higher burden to obstetric healthcare and higher costs.[28–30] Other critics of such a proposed change state that there is only limited evidence for the benefit of treatment of GDM diagnosed according to thresholds proposed by the IADPSG criteria (mild GDM), that the OGTT has poor reproducibility, and that data are lacking on the cost-effectiveness of GDM treatment when diagnosed according to the IADPSG criteria.[31,32]

The differences between the various guidelines in terms of cut-off levels indicate the need for large cost–benefit studies of the treatment of GDM diagnosed according to the

Table 1 Overview of the currently used diagnostic criteria for gestational diabetes mellitus worldwide

	WHO 1999[17]	WHO 2013,[14] IADPSG 2010[18]	ADA 2015[A,24]		NICE 2015[98]	ADIPS[112]	Carpenter and Coustan[26]	NDDG[27]
Glucose levels (mmol/L [mg/dL])								
Fasting	≥7.0 (≥128)	≥5.1 (≥92)	≥5.1 (≥92)	≥5.3 (≥95)	≥5.6 (≥100)	≥5.1 (≥92)	≥5.3 (≥95)	≥5.8 (≥105)
OGTT								
1-h	–	≥10.0 (≥180)	≥10.0 (≥180)	≥10.0 (≥180)		≥10.0 (≥180)	≥10.0 (≥180)	≥10.6 (≥190)
2-h	≥7.8 (≥140)	≥8.5 (≥153)	≥8.5 (≥153)	≥8.6 (≥155)	≥7.8 (≥140)	≥8.5 (≥153)	≥8.6 (≥155)	≥9.2 (≥165)
3-h	–	–	–	≥7.8 (≥140)	–		≥7.8 (≥140)	≥8.0 (≥145)
Total no. abnormal values	≥1[b]	≥1[b]	≥1[b]	≥2[c]	≥1[b]	≥1[b]	≥2[c]	≥2[c]

[a]The American Diabetes Association (ADA) 2015 recommendations leave the option open to use either the one-step International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommendation or the two-step strategy, with the option in the two-step strategy of using either the Carpenter and Coustan criteria or the National Diabetes and Data Group (NDDG) criteria.
[b]On a 75-g oral glucose tolerance test (OGTT).
[c]On a 100-g OGTT.
WHO, World Health Organization; NICE, National Institute for Health and Care Excellence; ADIPS, Australasian Diabetes in Pregnancy Society.

IADPSG criteria. Such studies may help overcome reluctance for a broad implementation of strict diagnostic criteria. Because the main reason for this reluctance currently appears to be economic healthcare concerns regarding the burden of obstetric care, such studies will at least provide us with international consensus.

Treatment

Two randomized controlled trials (RCTs) have investigated the benefits of screening and treatment of GDM in terms of pregnancy complications.[11,12] The first was conducted in 2005 by the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group.[12] That study randomly assigned 1000 women with GDM between 24 and 34 weeks gestation to receive either dietary advice, self-monitoring of blood glucose (SMBG), and insulin therapy (intervention group) or routine care (control group). Women in the routine care (control) group replicated clinical care in which screening for GDM was not available. The study showed that treatment of GDM reduced the frequency of serious perinatal complications (defined as perinatal death, shoulder dystocia, bone fracture, and nerve palsy) and improved the mother's health-related quality of life.[12] However, the women in the intervention group were more likely to have labor induced than women in the routine group, and more of the neonates in the intervention group were admitted to the neonatal nursery.[12]

The second RCT was conducted in 2009 by Landon et al.[11] and included 958 mild GDM pregnancies (defined as a fasting glucose <5.3 mmol/L) between 24 and 31 weeks gestation. The women were assigned to usual prenatal care (control group) or dietary advice, SMBG, and insulin therapy (intervention group). The study showed that although treatment of mild GDM did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death and several neonatal complications, it did reduce the risk of fetal overgrowth, shoulder dystocia, cesarean delivery, and pregnancy hypertensive complications.[11]

Following on from these findings, several systematic reviews and meta-analyses summarized the evidence of the benefits of treatment for women with GDM.[33–37] These reviews included mainly the aforementioned trials, but also additional studies that compared intensive treatment, including diet modification, glucose monitoring, and/or insulin, or any therapeutic intervention of GDM with usual obstetric care in women with GDM. These reviews demonstrated not only that treatment of GDM is effective, but that it also lowers the risk of pre-eclampsia and several neonatal complications, including macrosomia, shoulder dystocia, and neonates born large for gestational age (LGA).[33–37]

Diet

Globally, the primary approach for GDM is dietary advice in combination with SMBG. It is estimated that dietary advice helps 70%–85 % of women with GDM to obtain optimal glycemic control.[38] Remarkably, there are no specific guidelines for diet or exercise in GDM. Nevertheless, there is consensus that the goal of dietary advice should be to fulfill nutrient intake for normal neonatal growth and to achieve optimal glycemic control, without inducing weight loss or excessive weight gain.[39] Optimal glycemic control can be achieved by following a diet that includes carbohydrate distribution and a reduction in rapidly digested sugars.

Increasing attention is being paid to the effect of different types of dietary intervention on pregnancy outcomes in women with GDM. Such specific dietary approaches include low-glycemic index (GI), energy restriction, and low-carbohydrate (LC) diets. A Cochrane systematic review on the effects of different types of dietary intervention in GDM found no effect for any specific type of dietary intervention in terms of reducing the following outcomes: instrumental deliveries, LGA neonates, or neonates with a birth weight > 4000 g.[40] However, this finding is in contrast with that of a more recent systematic review on the type of dietary interventions on maternal and neonatal outcomes in women with GDM.[41] That review included nine RCTs that had studied different types of dietary advice. The authors performed three meta-analyses according to the three types of dietary intervention: low-GI diets (defined as GI <55); total energy restriction diets (defined as 1600–1800 kcal or ~33 % reduction in caloric intake); and LC diets (<45 % of energy supply coming from carbohydrates). When the dietary interventions were compared with the control diets, only a low-GI diet was associated with beneficial outcomes, such as less frequent insulin use and lower neonatal weight. The study suggested that a low-GI diet reduces the use of insulin because of its ability to reduce postprandial glucose excursions.[41]

Apart from these meta-analyses on dietary interventions, the role of LC diets in GDM has gained considerable attention. Low-carbohydrate diets are currently popular in the general population and are widely used to treat obesity.[42] Evidence has shown that LC diets are also effective in the treatment of diabetes, particularly if the condition is complicated by insulin resistance.[43,44] Consequently, more attention is being paid to the use of an LC diet in GDM. However, evidence is lacking on both the short- and long-term effects of an LC diet in GDM, in terms of both blood glucose values and safety.

According to the National Academy of Medicine, the minimum daily carbohydrate intake should be >130 g for the general population and >175 g for pregnant women.[45] The additional 45 g/day carbohydrates are indicated for neonatal brain development and functioning. A carbohydrate intake <175 g can have negative consequences for the neonate.[46] Furthermore, to compensate for the reduced carbohydrate intake, the intake of other sources of nutrients, such as protein and fat, increases. Because of an LC diet's restricted food choices, there is an increased risk of nutritional deficiencies. Therefore, such diets may theoretically limit the consumption of dietary fiber, vitamins, calcium, potassium, magnesium, and iron.[47]

Two RCTs[48,49] and one non-randomized trial[50] that investigated the short-term effectiveness of an LC diet in GDM reported conflicting results. Two of the studies showed postprandial glucose values were lower in women on an LC diet (ranging from 40 % to 45 % in the intervention group) than in women on a high-carbohydrate diet (ranging from >45 % to 65 % in the control group).[49,50] Although neither of these studies reported a reduction in fasting glucose values, in the study by Major et al.[50] the women with the lowest carbohydrate intake (<42 %) required less additional insulin therapy. However, in the RCT by Moreno-Castilla et al.,[48] an LC diet (intervention 40 % vs control 55 %) did not significantly reduce the need for insulin therapy.

A recent prospective cohort study in women with a history of GDM[51] investigated whether there was an association between an LC diet and the long-term risk of type 2 DM (T2DM). An LC diet with a high intake of protein and fat mainly from animal-based foods was associated with a higher risk of T2DM, whereas an LC diet with a high intake of protein and fat mainly from plant-based foods was not. These findings suggest that women with a history of GDM who follow an LC diet may reduce their future risk of T2DM by consuming plant- rather than animal-based sources of protein and fat.[51]

In summary, there is general agreement on limiting excessive carbohydrate intake and that carbohydrates should be distributed equally throughout the day. Although it is unknown whether carbohydrate restriction is beneficial in GDM, some studies have shown beneficial effects on glucose control and also on the risk of developing T2DM after GDM.

Insulin

Women who receive dietary advice but fail to maintain glycemic control within 1–2 weeks generally receive additional insulin therapy. Insulin therapy is the medication of choice in GDM and is recommended in almost all international guidelines. Insulin is safe in pregnancy because it virtually does not cross the placental barrier and it is not known to have any teratogenic effects. The most frequently used types of insulin are regular insulin (RI) and neutral protamine Hagedorn (NPH) insulin, which are both completely homogeneous with human insulin and therefore considered safe in pregnancy. A major drawback of RI is that its activity profile does not match that of physiological insulin. The onset of action of RI begins between 30 and 60 min after injection, reaching peak activity after 2–3 h and having an effective working duration lasting up to 8–10 h.[52] Not only does it often peak too late to control postprandial blood glucose values, but it also carries an increased risk of hypoglycemia. To overcome this, rapid-acting insulin analogs have been developed in which one of the amino

acids is substituted to improve the pharmacokinetic profile. The action of rapid-acting insulin analogs (i.e. lispro, aspart, and glulisine) begins 5–15 min after injection, reaching peak activity between 30 and 90 min and having an effective working duration of 4–6 h.[52] Rapid-acting insulin analogs can therefore help achieve good postprandial blood glucose values while minimizing the risk of hypoglycemia.[52]

Both insulin aspart and lispro have been shown to be effective in pre-existing DM but have not been studied extensively in GDM.[53–55] To date, few studies have looked specifically at aspart and lispro in GDM.[56–61] A review by Lambert and Holt[62] on the use of insulin analogs in pregnancy showed that compared with RI, the use of aspart and lispro is associated with better maternal glycemic control and a similar fetal outcome. No evidence of increased risk of congenital anomalies has been reported.[63] Because insulin aspart and lispro are licensed for use during pregnancy in Europe, both insulin lispro and insulin aspart can be safely administered in pregnancy.

The use of NPH and the long-acting basal insulin analogs has both advantages and disadvantages. A major drawback of NPH insulin is that both its duration of action and peak effect are intermediate. The action of NPH begins 2–4 h after injection, its peak action effect is between 4 and 10 h, and its effective working duration is 12–18 h.[52] Indeed, outside pregnancy, rates of nocturnal hypoglycemia are known to be higher for NPH insulin than for long-acting analogs.[64] The onset of action for long-acting insulin analogs is 2–4 h after injection and their effective duration is 16–20 h, with no peak effect.[52] Insulin detemir has been approved by the US Food and Drug Administration (FDA) for use during pregnancy,[65] and its use has shown no adverse pregnancy outcomes.[66] The data on insulin glargine in pregnancy appear to be insufficient because most of the studies that have included this drug are small and retrospective.[62] Furthermore, insulin glargine has insulin-like growth factor (IGF)-1-binding properties, which could be a disadvantage in pregnancy.[63,67] However, as for RI, insulin glargine does not to cross the placental barrier.[68] There is no evidence to support the use of insulin glargine in GDM.

Oral blood glucose-lowering agents

In recent years, the use of oral blood glucose-lowering agents has gained considerable interest as an alternative for insulin therapy during pregnancy. Oral agents are not only less expensive, but they are also more easy to use, making them more patient friendly than insulin therapy, which requires training in insulin injection technique and demands time of healthcare providers.[69] It has been suggested that the oral blood glucose-lowering agents glyburide and metformin can be used in pregnancy.

Glyburide is a second-generation sulfonylurea (SU) that directly stimulates insulin secretion by binding to the SU receptor on the cell membrane of pancreatic β-cells. The major side effects of glyburide are an increased risk of maternal hypoglycemia and weight gain. There was a long-standing controversy as to whether glyburide can cross the placental barrier. In earlier studies glyburide, was not detected in the cord blood of the neonates,[70,71] but this was rejected by a later study that reported detecting glyburide in the cord blood at concentrations around 70 % of those in maternal blood.[72]

Metformin is a biguanide blood glucose-lowering agent that acts by reducing hepatic gluconeogenesis. In contrast with glyburide, metformin does not carry an increased risk of hypoglycemia and weight gain. Metformin is known to cross the placental barrier, with the fetus being exposed to levels of metformin similar to those in the mother.[73]

Short-term effects of glyburide

The first major RCT to compare glyburide and insulin in GDM was conducted by Langer et al. in 2000.[71] In total, 404 women with GDM between 11 and 33 weeks gestation were randomly assigned to receive glyburide or insulin. The primary endpoint was glycemic control and the secondary endpoints included perinatal complications. Glycemic control and perinatal outcomes were similar in both groups. There was less maternal hypoglycemia in the glyburide group (2 % vs 20 %). In 4 % of women in the glyburide group, this medication failed to produce good glycemic control, and these women needed additional insulin.[71]

Since the RCT by Langer et al., numerous trials and cohort studies have investigated the effects of glyburide in GDM. A recent and well-conducted meta-analysis by Balsells et al.[74] summarized the short-term outcomes of RCTs that compared glyburide or metformin with insulin or with each other. The analysis included seven trials that compared glyburide with insulin and demonstrated that glyburide was associated with a higher birth weight, an almost threefold higher risk of macrosomia, and a twofold higher risk of neonatal hypoglycemia.[74] The findings of Balsells et al.[74] are comparable with those of an earlier meta-analysis conducted by Zeng et al.[75] However, this earlier study concluded that glyburide is as effective as insulin, while also reporting a higher risk of neonatal hypoglycemia, high birth weight, and macrosomia.[75]

Balsells et al.[74] only included two studies that compared metformin with glyburide and found metformin

to be associated with less maternal weight gain, lower birth weight, less macrosomia, and fewer LGA neonates. Metformin was associated with slightly higher fasting blood glucose levels and higher treatment failure compared with glyburide.[74]

In summary, the evidence available from clinical studies does not support the use of glyburide in GDM, especially if metformin or insulin is available.

Short-term effects of metformin

Since 2007, evidence for the efficacy and safety of metformin use in pregnancy has been reinforced by the results of several RCTs and meta-analyses.[74,76–80] In 2013, the first meta-analysis was conducted by Gui et al.[76]; this study included five RCTs[81–85] that compared the effects of metformin with those of insulin therapy in terms of glycemic control and maternal and neonatal outcomes in GDM. Although Gui et al.[76] reported no differences between metformin and insulin in terms of glycemic control and neonatal outcomes (birth weight, LGA neonates, hypoglycemia, shoulder dystocia, and cesarean delivery), rates of preterm birth were found to be increased for metformin. Conversely, compared with insulin therapy, metformin was associated with less maternal weight gain and lower rates of pregnancy-induced hypertension, the latter thought to be explained by insulin-mediated sodium retention.[76]

Recently, five other meta-analyses have been published comparing metformin and insulin therapy in GDM.[74,77–80] The meta-analyses by Poolsup et al.,[77] Balsells et al.,[74] and Gui et al.[76] included the same RCTs and found comparable results. The main difference between these meta-analyses was that Poolsup et al.[77] and Balsells et al.[74] included an additional RCT[86]; they also did not address exactly the same outcomes: Poolsup et al.[77] had no information on maternal weight gain and Balsells et al.[74] added additional outcomes, including severe neonatal hypoglycemia and maternal total weight gain. In this respect, Balsells et al.[74] reported lower occurrence of severe neonatal hypoglycemia and a lower maternal total weight gain in the metformin group. The other three meta-analyses[78–80] included the aforementioned RTCs as well as additional RCTs.[87–89]

On the basis of current evidence, it seems that metformin may have some benefits with short-term neonatal outcomes similar to those for insulin therapy. However, the higher risk of preterm birth in metformin treatment is a point of concern that should be addressed in further studies.

Long-term effects of metformin

Unfortunately, little is known about the long-term effects of metformin in GDM. To date, several studies have investigated the long-term effects of metformin use in pregnancy on the subsequent growth and development of the children.[90–93] In 2011, the results of a 2-year follow-up study of offspring were reported by the Metformin in Gestational Diabetes (MiG) Trial. The aim of that study was to compare the results of metformin and insulin treatment in terms of body composition and measures of adiposity in the children of women who participated in the MiG trial.[83,92] Children who were exposed to metformin in utero had larger subscapular and biceps skin folds than the offspring of mothers who received insulin. The study suggests that metformin use is associated with more fat being stored in subcutaneous sites and perhaps less accumulation of ectopic or visceral fat.[92] The study found no difference in total or percentage body fat between the children exposed to metformin or insulin.[92] One other follow-up study found that children exposed to metformin were heavier at the age of 12 months and were both taller and heavier at 18 months.[90] However, in the multivariate regression analysis, maternal body mass index (BMI) was the only risk factor predicting a child being overweight or obese at the age of 18 months. Compared with insulin exposure, the study found no adverse effects of prenatal metformin exposure on motor, linguistic, or social development of the offspring during the first 18 months of life.[90]

Another two follow-up studies of offspring and their mothers were from an RCT conducted in women with polycystic ovary syndrome who had been treated with metformin or placebo during pregnancy.[91,93] The first study,[93] with a 1-year follow-up, showed that women who received a placebo during their pregnancy had lost more weight and had a lower BMI 1 year after delivery than women who received metformin during their pregnancy. However, the women in the metformin group gained less weight during their pregnancy. The offspring exposed to metformin in utero had a higher body weight at 1 year of age than those exposed to placebo.[93] In another study,[91] the same authors performed a small follow-up study of the offspring at the age of 8 years. At that age there were no differences in height, weight, body composition, and insulin resistance. However, the children exposed to metformin in utero had higher fasting glucose levels, higher systolic blood pressure, and lower low-density lipoprotein cholesterol.[91]

There appears to be an urgent need for longer follow-up studies assessing the true effect of metformin in a larger offspring cohort at least until adolescence or adulthood.

Studies on the effects of metformin during pregnancy in humans have reported no harmful effects or teratogenicity.[94,95] However, animal studies have shown that

metformin may harm the male reproductive system. Tartarin et al.[96] investigated both testicular development and function in the offspring of mice administered metformin during pregnancy. As well as analyzing embryonic mice testes in vivo, that study included human and mouse in vitro models. The results showed that, in vitro, metformin reduced testosterone secretion by decreased mRNA expression involved in steroid production. In vivo, the number of Sertoli cells was slightly reduced. The number of Leydig cells, which produce androgens, including testosterone, was diminished in the fetal period. The study showed that metformin has detrimental effects on the developing fetal testis.[96]

Other studies on the possible endocrine-disrupting effects of metformin on male reproduction have been performed in adult male fish. Because metformin is a widely used medication in T2DM patients and is not metabolized by the human body, high amounts are commonly found in wastewater and surface water. The medication is apparently not fully removed by wastewater treatment processes and is thought to be affecting the health of fish populations. Recent studies have shown that metformin can cause intersex in fish and cause male fish to produce eggs.[97] This environmental pollution clearly illustrates that more studies are needed to investigate the possible endocrine-disrupting effects of metformin on vertebrate development and male fertility.

Despite the fact that the use of metformin in GDM is questionable, especially because of the lack of long-term safety data in offspring, metformin has already been incorporated into at least two sets of guidelines. The National Institute for Heath and Care Excellence (NICE) guideline (UK) recommends the use of metformin or insulin if lifestyle interventions fail to control glycemic levels[98]; the American College of Obstetricians and Gynecologists guideline also recommends the use of metformin in GDM.[99]

Long-term effects of GDM

In recent years there has been increasing concern that GDM may also be associated with long-term consequences for the mother and child. Metabolic changes in the mother during pregnancy can lead to structural and functional adaptations during the development of the fetus, with potential consequences for growth and metabolism in the child's later life. This phenomenon is called fetal programming and was first introduced by Hales and Barker.[100] These authors found that babies who grow less well due to starvation in utero were more likely to become overweight and develop T2DM and cardiovascular diseases in adulthood.[100]

To date, several studies have investigated the association between maternal diabetes and the consequences for offspring in later life. These studies have predominantly shown that maternal diabetes is associated with obesity and T2DM in the offspring in later life.[8,101–103] Animal models have also shown that intrauterine exposure to mild maternal DM during pregnancy is associated with T2DM, insulin resistance, and obesity in the offspring.[104] However, in animal studies it is easier to study the precise effect of maternal glucose levels on fetal development than in human studies. It is also easier to control for the main confounders, such as genetic susceptibility and postnatal environmental influences.

Several systematic reviews have summarized evidence from studies on the long-term consequences for offspring of women with GDM. However, in terms of an association between GDM and overweight and obesity in the offspring, the results of the reviews were inconsistent.[105,106] In a recent critical review by Donavan and Cundy,[107] there was no robust evidence found that exposure to hyperglycemia in utero increases the risk of obesity and diabetes in the offspring. These authors suggested that the increased risk of obesity seen in the offspring of women with GDM may be explained by confounding factors, such as parental obesity (Fig. 1).

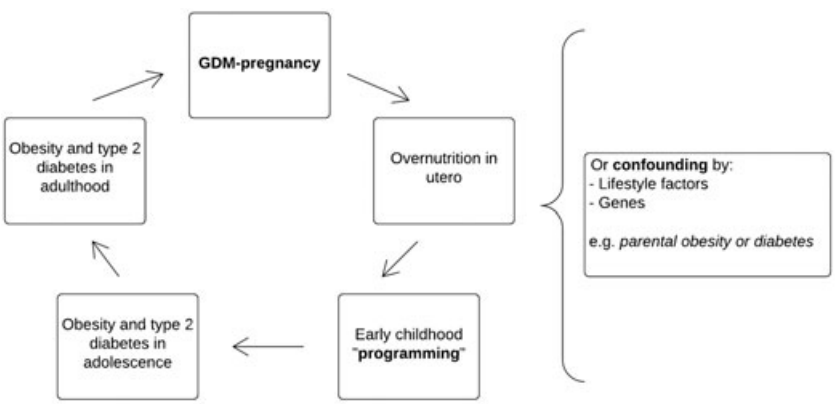

Figure 1 Fetal programming in gestational diabetes mellitus. GDM, gestational diabetes mellitus; T2DM, type 2 diabetes mellitus.

There is a need for more research into GDM, and especially for long-term studies into the programming and development of offspring who have been exposed prenatally to mild or moderate hyperglycemia that include adequate controls for confounding factors.

Even though in most women with GDM glucose values normalize after delivery, it is well known that women with a history of GDM are at increased risk for impaired glucose tolerance and for developing T2DM postpartum.[108–110] Studies have shown that the risk of developing T2DM may be as high as 50 % in the 5–10 years after GDM.[108,109] Therefore, it is important that we recognize persistent glucose intolerance and diagnose T2DM as early as possible in these women in order to start early interventions and to prevent long-term DM complications. Prevention strategies, such as lifestyle interventions, could have a considerable positive public health impact.[111]

Future directions and challenges

There is clearly a need for more GDM research. Gestational diabetes mellitus is a global health problem, not only because its prevalence is high and on the increase, but also because of the potential implications for the health of mothers and their offspring. There is a clear need for a set of globally uniform guidelines on the diagnosis of and treatment strategy for GDM. Currently, guidelines differ with regard to diagnostic cut-off criteria, most likely prompted by the fear of the costs and healthcare efforts that would be attached to any strengthening of diagnostic criteria. Endeavors to adopt the criteria proposed by IADPSG will warrant large cohort studies in GDM in order to provide both medical and economic justifications for such a change.

The treatment of GDM is also accompanied by both certainties and caveats. There is no specific guideline on dietary treatment and studies are scarce, although there is general consensus that excessive carbohydrate intake should limited and distributed over meals to lower glycemic excursions. However, it is unknown whether carbohydrate restriction is actually beneficial in GDM, as has been indicated by a number of studies on this topic. Although these studies showed promising results on glycemic control and the reduced risk of later developing T2DM, there is a clear need for further investigating the benefits and perils of carbohydrate restriction in GDM both during pregnancy and afterwards.

With the exception of specific issues related to the use of insulin in GDM, drug treatment remains contentious and the advice provided in guidelines is highly variable. In terms of the use of oral blood glucose-lowering agents, the risk of neonatal hypoglycemia and increased neonatal birth weights does not support use of glyburide in GDM. The use of metformin seems promising and has already been incorporated into several guidelines. The uncertainties related to metformin use are a possible risk of premature delivery and concerns of the long-term safety regarding male fertility, and there is a particular need for studies regarding fetal programming and development in the offspring.

Acknowledgements

The author's work reported herein was supported by an unrestricted research grant from Novo Nordisk Netherlands.

Disclosure

The authors have nothing to declare.

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